The NeuroNEXT Central IRB Model

SACHRP, October 10, 2012

P. Pearl O'Rourke, M.D.

Partners Health Care

Life would be grand!
If I only had a central IRB!

Agenda

- Suggested classification of ‘central’ IRBs
- The NeuroNEXT model
  - Specific elements that facilitate/d the process
  - The model itself
- The process getting there
- Challenges encountered
  - ‘Solutions’ implemented

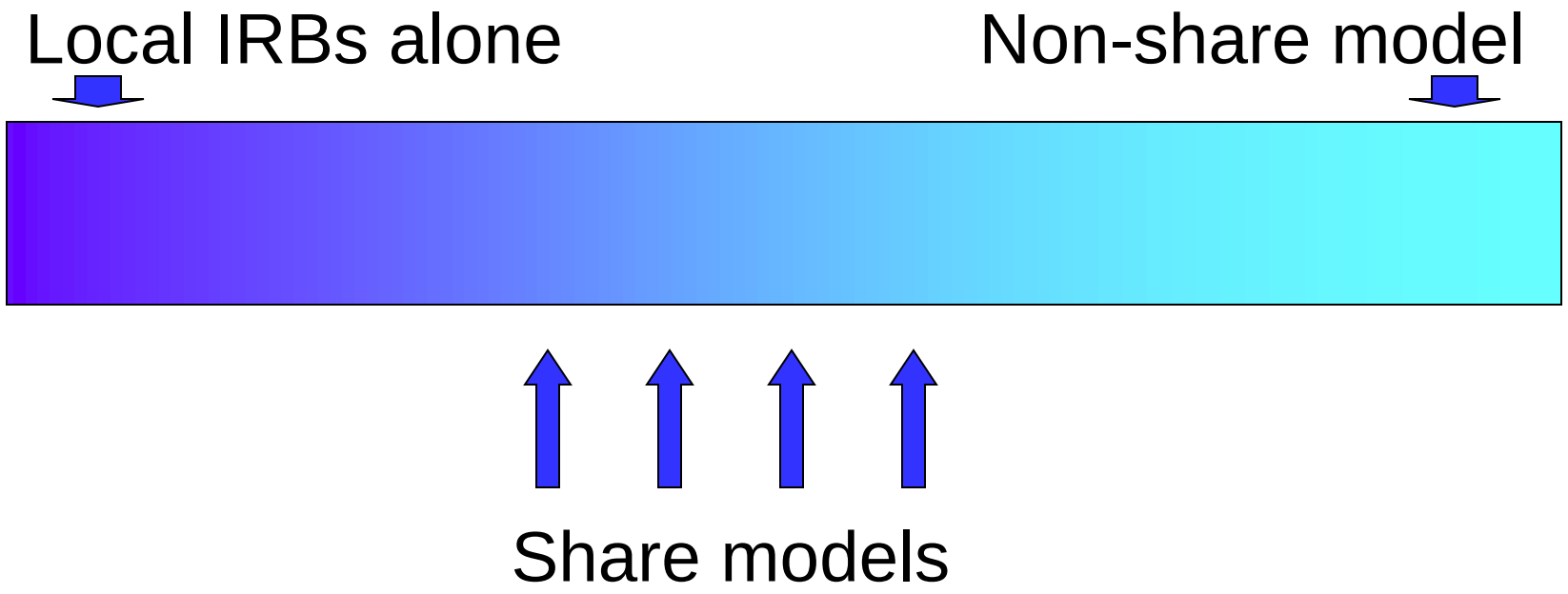
Agenda

- Suggested classification of ‘central’ IRBs
- The NeuroNEXT model
  - Specific elements that facilitate the process
  - The model itself
- The process getting there
- Challenges encountered
  - ‘Solutions’ implemented

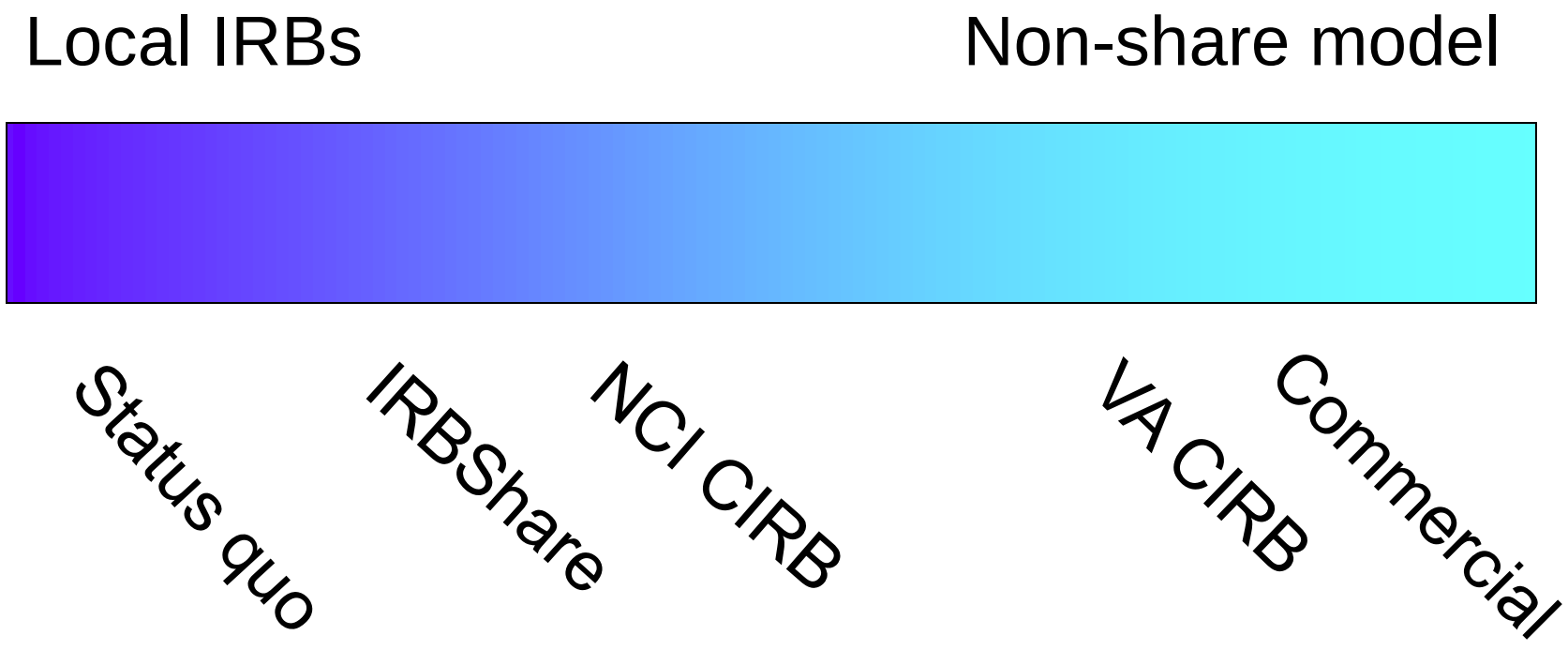
Models of Central IRBs

- Non-share model
  - Central IRB fulfills all IRB-review requirements
- Share model
  - Central IRB and local IRB share review responsibilities

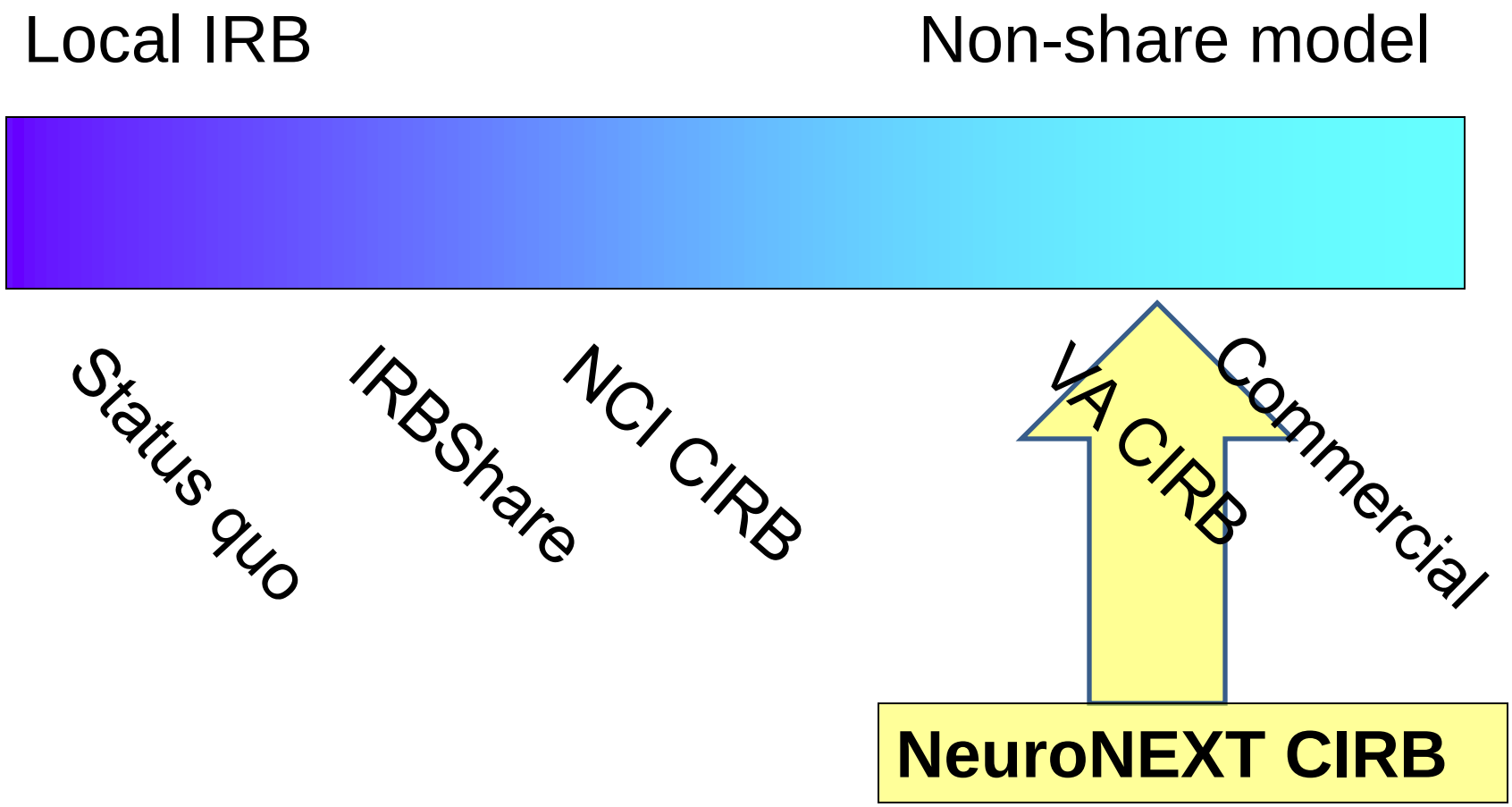
Proposed taxonomy of Central IRBs



Proposed taxonomy of Central IRBs



Proposed taxonomy of Central IRBs



Agenda

- Suggested classification of ‘central’ IRBs
- The NeuroNEXT model
  - Specific elements that facilitate/d the process
  - The process itself
- Process getting there
- Challenges encountered
  - ‘Solutions’ implemented

NeuroNEXT CIRB

- Non-share model
  - CIRB conducts all IRB-reviews
- CIRB agreement prior to site selection

The NeuroNEXT CIRB
-Background-

- NINDS grant to support a network of 25 academic centers to facilitate clinical trials in neurology
- RFA indicated preference for sites agreeing to use a central IRB process
  - RFA included three tiers
    - CIRB only
    - Facilitated model
    - Local IRB
- At funding – CIRB only was selected

NINDS website - NeuroNEXT

- “One particularly innovative aspect of NeuroNEXT is the use of a common IRB that should significantly decrease the time between trial design and initiation while ensuring patient safety.”

http://www.ninds.nih.gov/about_ninds/message/message-NeuroNEXT.htm

Important to note:

We had the luxury of NN ‘Safety Nets”

- Comprehensive NeuroNEXT infrastructure
  - Study design process
  - Clinical Coordinating Center
    - A dedicated CIRB-CCC liaison person
  - Data Coordinating Center
  - Research Pharmacy
  - Education and site-monitoring
  - Robust SOPs
- NINDS staff support

The NeuroNEXT CIRB

- CIRB had to be situated at the same site as the CCC (clinical coordinating center)
  - Massachusetts General Hospital = CCC
  - Therefore, the Partners* (PHS) IRB becomes CIRB

* MGH and BWH collaborate in a singe IRB system under PHS

The NeuroNEXT CIRB
Additional info

- While the 25 NeuroNEXT sites are the expected study sites
- Additional sites may be added:
  - Investigators from non-NeuroNEXT sites can propose studies to be done by NeuroNEXT
  - Non-NeuroNEXT sites may be invited to join specific studies as needed
    - E.g. for rare diseases

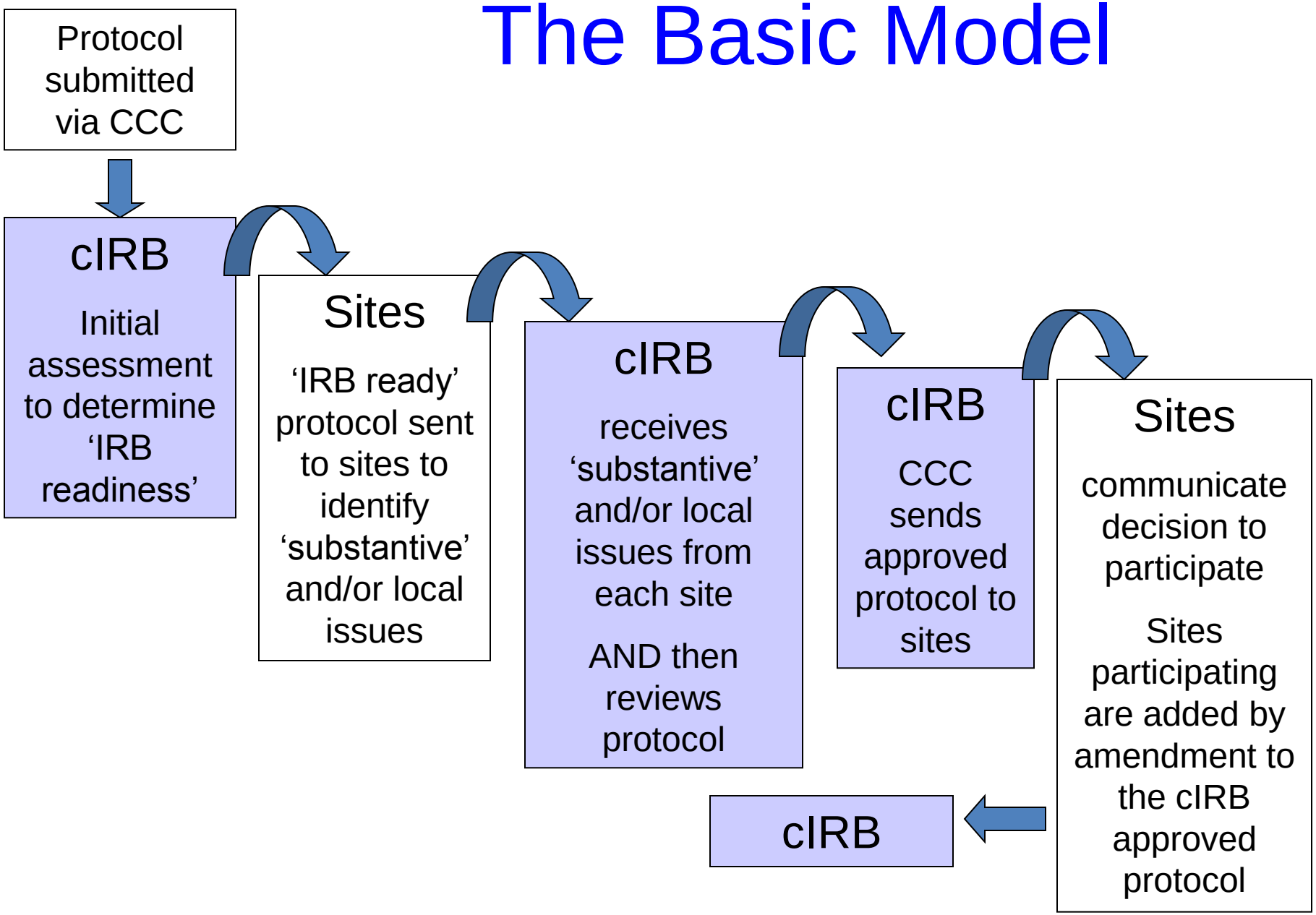
The NeuroNEXT CIRB
Additional info

- While the 25 NeuroNEXT sites are the expected study sites
- Additional sites may be added:
  - Investigators from non-NeuroNEXT sites can propose studies to be done by NeuroNEXT
  - Non-NeuroNEXT sites may be invited to join specific studies as needed
    - E.g. for rare diseases
- Therefore system must accommodate:
  - Stable group of participating sites as well as
  - ‘One-offs’

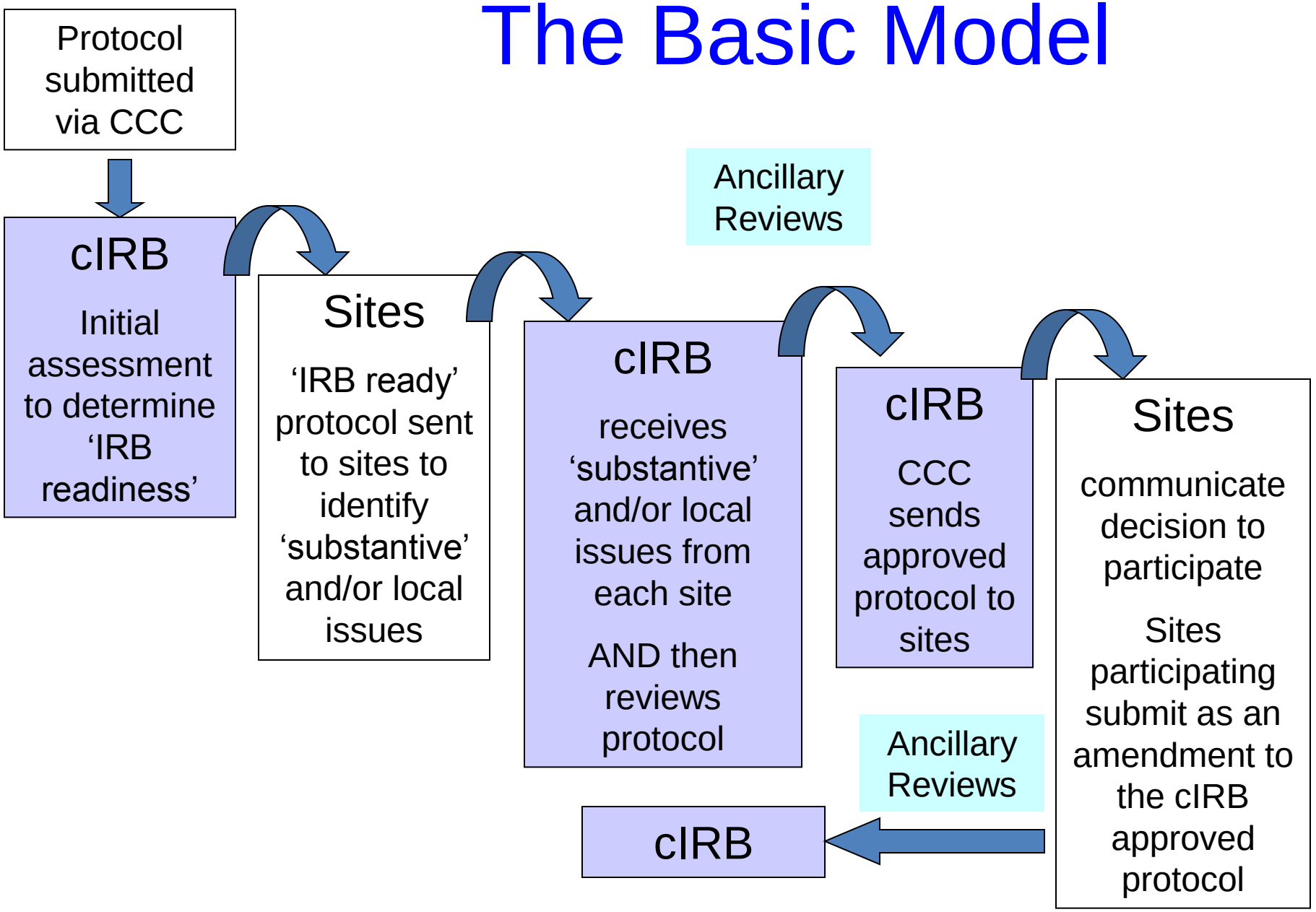
The model

- Single CIRB – nonshare
  - PI-site submits ‘parent’ protocol for CIRB review
  - After approval of ‘parent’ protocol, additional sites are added as amendments

The Basic Model



The Basic Model



“Parent-protocol” review

- PI submits protocol to CIRB
- CIRB reviews for ‘IRB-readiness’
- ‘IRB-ready’ protocol is sent to all sites that are interested in participating
- Sites have 2 weeks to conduct institutional review and submit comments
  - re: the protocol in general as well as local context issues
- CIRB conducts PI protocol review
  - Incorporates feedback from local sites
- PI coordinates ancillary review/s for PI-site and submits to the CIRB
- CIRB can then approve the protocol

Conflict of Interest

- The CIRB will consider COI issues in the approval of the protocol and will include management plan/s.
  - E.g., disclosure in the ICF
- Each local site:
  - Applies local standards and processes
  - Can mandate more stringent management than required by the CIRB.
  - Cannot implement less stringent management
- COI subcommittee of NN-Exec.Com.
  - Resource for the CIRB

ICF: (with NeuroNEXT header)
PI develops:

- A model ICF that includes:
  - Locked portion, e.g.
    - Study procedures
    - Risks and benefits
  - Customizable portion, e.g.
    - HIPAA
    - COI language
    - Injury language
    - Contact persons
- A PI-site-specific ICF that includes:
  - Locked portion and completed customizable portion

HIPAA

- CIRB will:
  - Make HIPAA determinations
  - Incorporate authorization language into the consent form
- Local sites can use:
  - cIRB developed ICF that includes authorization
  - Insert their own authorization language into the ICF in lieu of authorization language in CIRB ICF*
  - Use their own free-standing authorization in lieu of authorization language in CIRB ICF*

** Final ICF and authorization must be submitted to and approved by the CIRB*

“Child-protocol” review

- CIRB approved protocol is sent to each interested site
- Each site makes final decision re: participation
- Each site will be reviewed as an amendment to the ‘parent-protocol’ and must submit:
  - Evidence of local ancillary review/s
  - A completed ICF that includes:
    - Locked portion
    - Customizable portion that includes local ICF content

After the protocol is CIRB approved
Continuing Review

- Anniversary date for all participating sites is tied to the parent protocol approval
- Each site PI submits site-specific continuing review data to CCC-CIRB liaison who collates and submits to the CIRB

After the protocol is CIRB approved

Adverse events/UAPs, Deviations, Complaints, Changes to Eliminate Immediate Hazards, Non-Compliance, and Suspension or Cessation of Study

- Each site PI submits site-specific reports to CCC-cIRB liaison who will submit to the CIRB
  - If an issues requires notification of all sites, the CIRB will communicate same via the CCC

After the protocol is CIRB approved

Amendments

- Each site PI submits site-specific amendments to CCC-CIRB liaison for submission to the CIRB
  - Site-specific amendments limited to:
    - Administrative (e.g., study staff changes) and requests for protocol exceptions;
  - Any amendment that substantively changes the study must be coordinated through the PI-site and CCC
  - Issues identified as a result of CIRB review of amendments requiring notification of all sites will be sent out from the CIRB via the CCC-CIRB liaison

Agenda

- Suggested classification of ‘central’ IRBs
- The NeuroNEXT model
  - Specific elements that facilitate/d the process
  - The model itself
- The process getting there
- Challenges encountered
  - ‘Solutions’ implemented

The Process

- Request for and review of site information
- Develop a draft reliance agreement for
  - NN member sites
  - ‘One-offs’
- Review of draft reliance agreement
  - Sent electronically
  - Two webinars
- Negotiate individual reliance agreements
- Simultaneously working on SOPs with NN leadership
- Modify our electronic IRB system for accommodating this model

Site Information

- Organizational information
  - Relationship to researchers
  - Local research context
- HRPP description
  - IRB information
  - Accreditation status
- Copy of FWA
- Education requirements
- History of governmental inquiries/investigations
- HIPAA status
- Contacts

Reliance Agreement

- Establishes the PHRC as the IRB of record for HSR conducted as part of NeuroNEXT
- Delineates
  - The process of CIRB review
  - Assignation of legal, regulatory and contractual responsibilities

Reliance Agreement:
Institutional responsibility re: local context and ancillary review

- "Without limiting anything in the Reliance SOP, the eligibility of any specific Clinical Study for inclusion in this Agreement shall be contingent on **ABC**'s provision of complete information necessary to inform the Central IRB of **ABC**'s local research context as relevant to that Clinical Study. Such information shall include specific requirements of state or local laws, regulations, policies, standards or other factors applicable to **ABC** or the Clinical Study, as well as the conflict of interest information and relevant requirements of other local ancillary committee reviews…"

Reliance Agreements:
Compliance Investigations

- Compliance investigations will be the responsibility of each local institution
- The CIRB will have the right to initiate/conduct its own investigation in addition if necessary
- The expectation is one of collaboration and open communication with the CIRB, the CCC, the DCC and as appropriate, the sites
  - Findings of fact must be shared
  - Attorney-client privilege to be respected

Reliance Agreements:
External Reporting

- Logistics of external reporting will be determined on a case-by-case basis
- Site/s and the CIRB agree upon who will report
- Drafts and final reports will be shared between the relevant site/s and the CIRB
  - Allows either the CIRB or individual site/s to submit an additional report as deemed appropriate.
    - But presumption is that both parties will have the opportunity to review and comment on draft reports

Commitment Statement for Investigators
(two pages)

- Overview
  - Awareness of the CIRB use and relevant HSR requirements in general
- Reporting
  - Reminder of reporting requirements to the CIRB
- Other Responsibilities
  - PI is administratively responsible for all activities
  - Education and training
  - Compliance with SOPs
  - General HSR responsibilities

Reliance Agreements

- Prior to any protocol, all network sites must sign a reliance agreement with the CIRB
  - This RA will cover all NeuroNEXT studies
  - All RA's 'essentially' identical
- Non-member sites involved in NN-research must also sign the Reliance Agreement
  - Details remain the same, but the agreement is limited to a single protocol

The Reality

- Some reliance agreements signed within days of receipt
- Some required numerous discussions between the CIRB and the individual sites
  - See next section on challenges

Agenda

- Suggested classification of ‘central’ IRBs
- The NeuroNEXT model
  - Specific elements that facilitate/d the process
- The process getting there
- The model itself
- Challenges encountered
  - ‘Solutions’ implemented

Anticipated Challenges

- Differentiating between institutional and IRB tasks
- Obtaining and addressing local context
- Simple logistics of communication
- Developing trust
- …..

Anticipated Challenges

- Differentiating between institutional and IRB tasks
- Obtaining and addressing local context
- Simple logistics of communication
- Developing trust
- …..

IRB vs. Institution

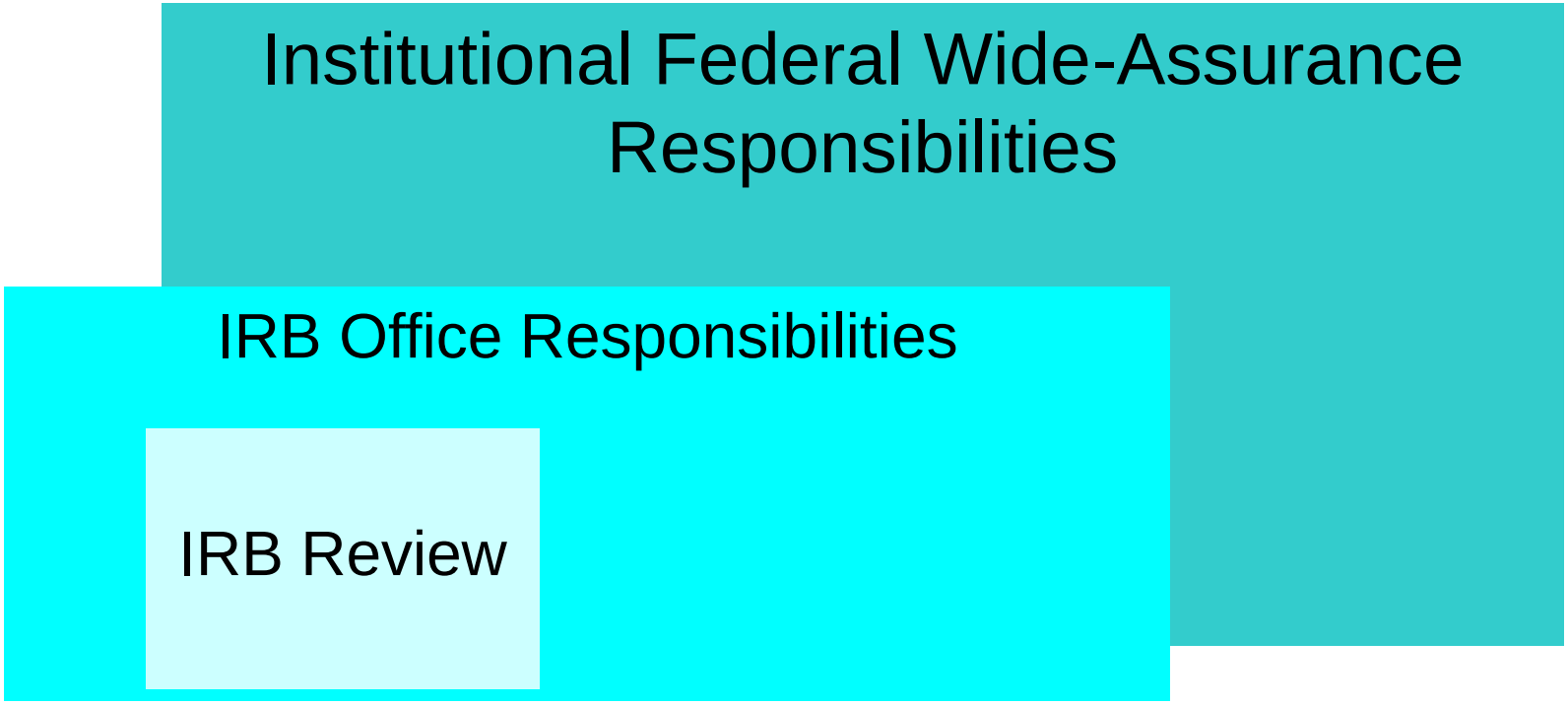
Institutional Federal Wide-Assurance Responsibilities

IRB vs. Institution

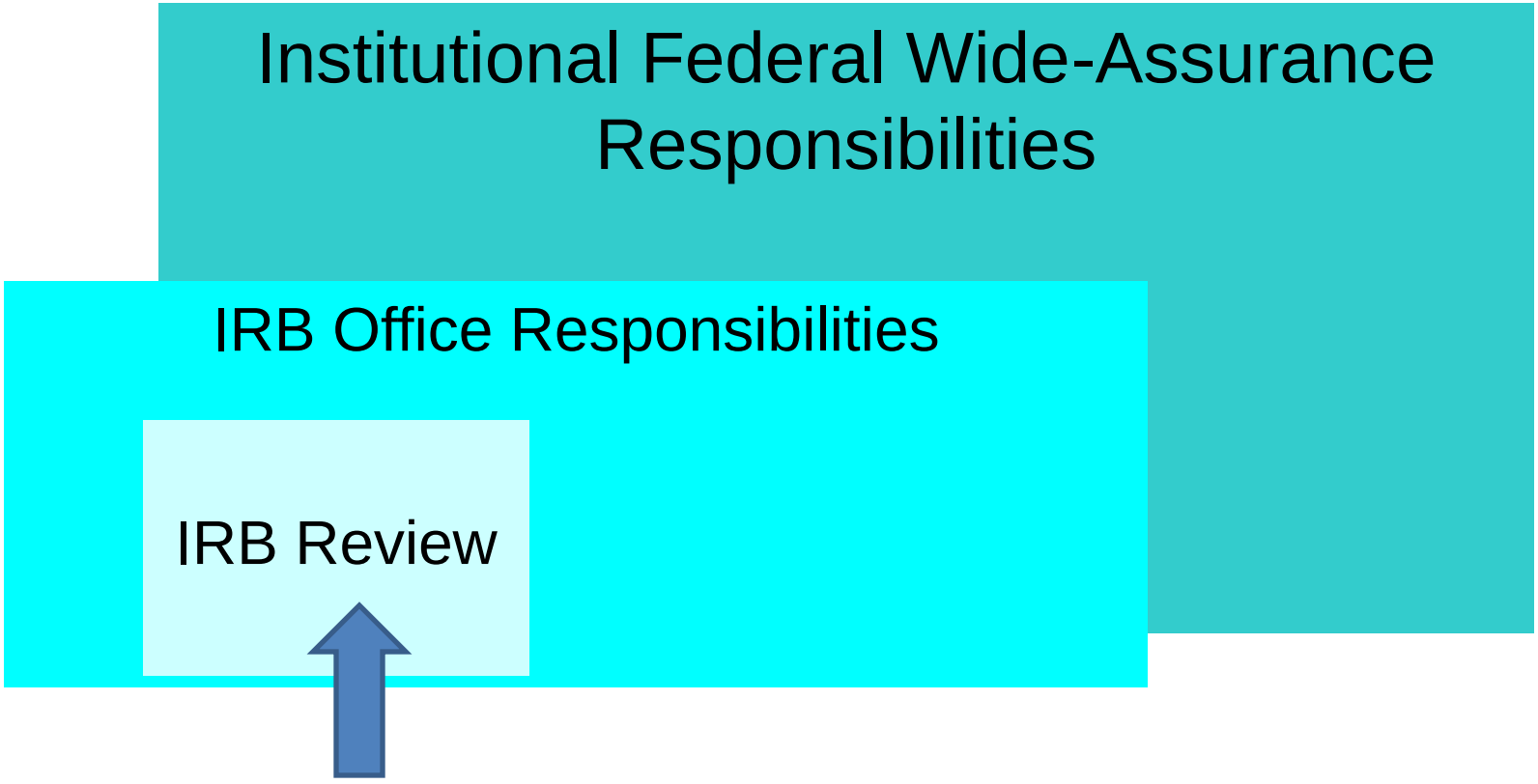
Institutional Federal Wide-Assurance Responsibilities

IRB Review

IRB vs. Institution



IRB vs. Institution



CIRB only to provide

NeuroNEXT CIRB

- CIRB responsibility
  - **All IRB review tasks**
    - Initial review
    - Continuing review
    - Amendments, deviations, AEs
  - HIPAA determination
    - Authorization
    - Waiver

- Local Site responsibility*
  - Site-specific context
    - E.g., Local laws
  - Ancillary review/s
    - E.g., Nursing, Rad'n safety
  - HIPAA implementation
  - Oversight of conduct of research
  - Required reporting

* ***Institutional NOT IRB review responsibility***

‘Solution’

- Remind all involved of:
  - FWA institutional responsibilities
  - IRB true-review responsibilities
  - HRPP responsibilities that are:
    - Not an IRB review responsibility
    - Assigned to/assumed by the IRB (Office)
- Developed and negotiated very detailed Reliance Agreements

The FWA

1. HSR must be guided by a statement of principles
2. Applicability

   "…apply whenever the **Institution** becomes engaged in human subjects research conducted or supported by any US federal department or agency that has adopted the Common Rule…"
3. Compliance with laws, regulations, policies and guidelines

The FWA

4. Written procedures

(a) "The **Institution**…has established written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the head of any US federal department or agency conducting or supporting the research (or designee) and OHRP of any:"

(1) UAP

(2) Serious or continuing noncompliance

(3) Suspension or termination of IRB approval

(b) "The **institution** will ensure that the IRB(s) that reviews research to which the FWA applies has established written procedures…"

Anticipated Challenges

- Differentiating between institutional and IRB tasks
- Obtaining and addressing local context
- Simple logistics of communication
- Developing trust
- …..

Local Context: ‘Solutions’

- Detailed Reliance Agreement and SOPs
- Investigator Commitment Statement
- Two week period for sites to review proposed protocol re: local issues as well as concerns/questions
  - Sites receive the protocol with a cover sheet that identifies specific issues that merit particular local review
    - E.g., minors in research; decisionally impaired, etc.
  - Conference calls for site discussion
- Customizable portion of the informed consent form
- Customizable HIPAA authorization format
- Protocol-specific Study Site Checklist

Anticipated Challenges

- Differentiating between institutional and IRB tasks
- Obtaining and addressing local context
- Simple logistics of communication
- Developing trust
- …..

‘Solutions’

- NOTE:
  - Perhaps more difficult given the fact that for NeuroNEXT, CIRB is expected for all NeuroNEXT trials.
- Allow local approach whenever possible

‘Solutions’

- NOTE:
  - Perhaps more difficult given the fact that for NeuroNEXT, CIRB is expected for all NeuroNEXT trials.
- Allow local approach whenever possible
- Maximize communication

- Conference calls
- IRB liaison
- Availability

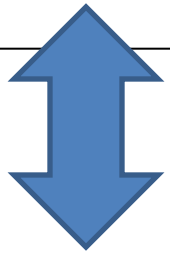
Unanticipated Challenges

- The complexity of member sites
  - Multiple subsites at which research would be conducted
  - Myriad organizational structures
- Lack of consensus on some basic issues
  - E.g., Engagement in research

Unanticipated Challenges

- The complexity of member sites
  - Multiple subsites at which research would be conducted
  - Myriad organizational structures
- Lack of consensus on some basic issues
  - E.g., Engagement in research

NeuroNEXT CIRB

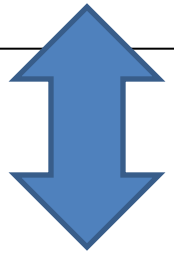


Reliance Agreement

NeuroNEXT

25 Prime sites

NeuroNEXT CIRB



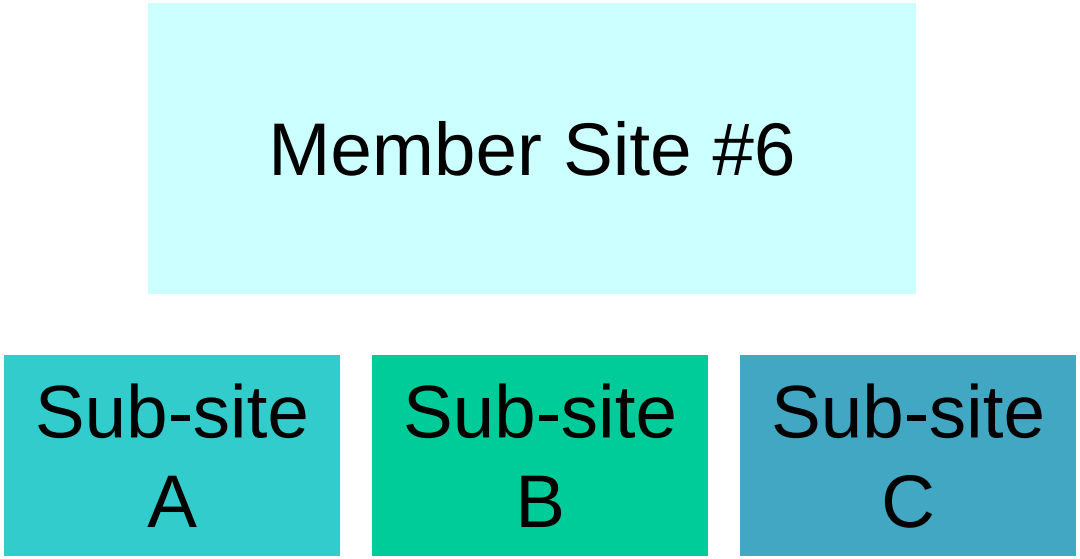
Reliance Agreement

NeuroNEXT

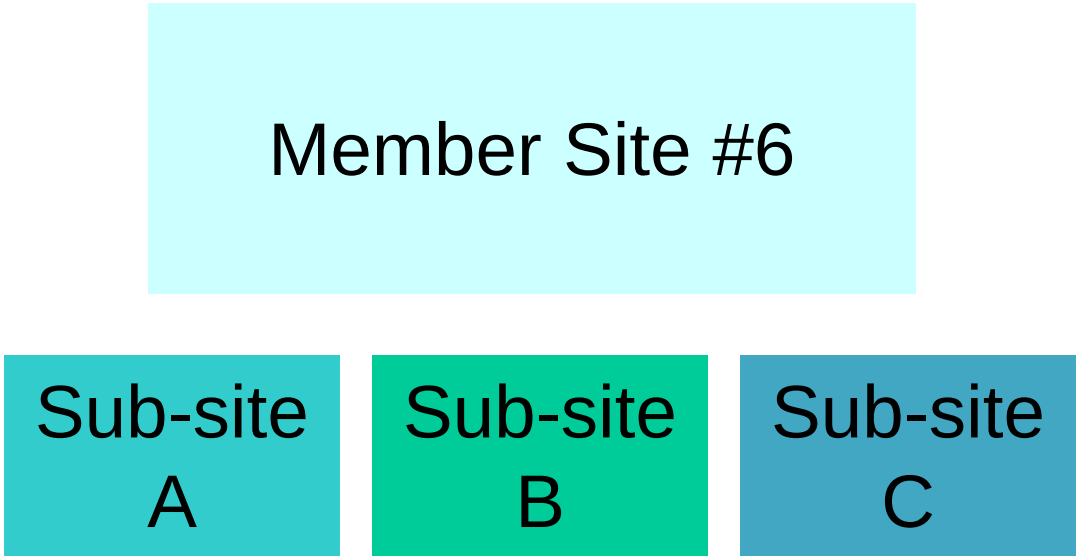
25 Prime sites

BUT…more than 40 subsites for a grand total of more than **60 sites**

Organizational Complexity



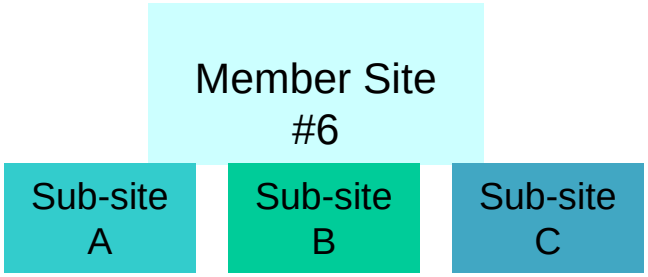
Organizational Complexity



Questions:

- What is the relationship between all entities?
- What is the HRPP structure?
    - How is/are IRB/s organized?
- What is the FWA status?

Organizational Complexity

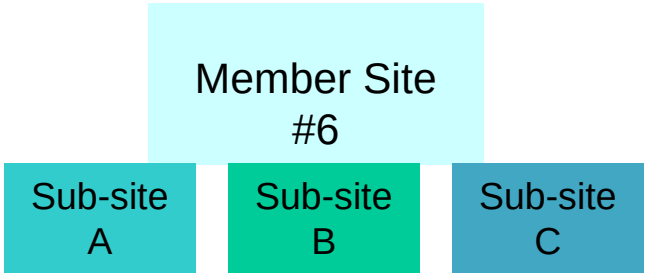


Straightforward scenarios encountered:

- Subsites A, B and C all in same city/complex as Member site 6
  - Same HRPP
  - Same IRB
  - One FWA

- Subsites A, B and C and Member site 6 all in different cities
  - Separate HRPPs
  - Separate IRBs
  - Separate FWAs

Organizational Complexity



Examples of less straightforward scenarios encountered:

- Subsites A, B and C and Member site 6
  - Same HRPP
  - Same IRB
  - Separate FWAs

- Subsites A, B and C and Member site 6
  - Same HRPP
  - Separate IRBs
  - Separate FWAs

‘Solution’

- Separate Reliance Agreement required for all sites and subsites with their own FWA
  - Regardless of relationship or existing reliance arrangements between Primary site and subsites.

The FWA

5. Institutional support for the IRB(s)
6. Reliance on an external IRB

> "Whenever the **Institution** relies upon an IRB operated by another institution or organization for review of research to which the FWA applies, the Institution must ensure that this arrangement is documented by a **written agreement between the Institution and the other institution or organization operating the IRB** that outlines their relationship and includes a commitment that the IRB will adhere to the requirements of the Institution's FWA."

NeuroNEXT CIRB

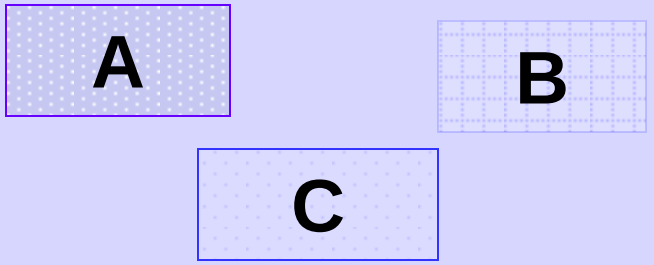
Reliance Agreement

NeuroNEXT

25 Prime sites

BUT…more than 40 subsites for a grand total of approximately **65 sites**

Non-NeuroNEXT Sites



Unanticipated Challenges

- The complexity of member sites
  - Multiple subsites at which research would be conducted
  - Myriad organizational structures
- Lack of consensus on some basic issues
  - E.g., Engagement in research

Engagement in Research

- Consider two affiliated Institutions A and B
  - They are separate legal entities
  - Professional Staffs at Institution A have privileges at B and vice versa
- Is Institution B 'engaged in research' if:
  - The PI from Institution A (with his privileges at Institution B) plans to:
    - Recruit participants from Institution B – but all study procedures will be done at Institution A?
    - Recruit participants AND perform the study procedures at Institution B?
      - Study procedures include: intravenous infusion of study medication and an MRI

‘Solution’

- Many phone calls and discussion with individual sites
- Implementation of a consistent approach

CIRB Goals

- Work collaboratively with local sites
  - Maximize communication and opportunity for input from local sites
- Provide high quality, efficient review for multiple sites
  - Efficiency likely to be gained in approval of ‘child’ sites
- Streamline continuing review, amendments and compliance reporting

CIRB - Lessons Learned

- Don’t underestimate:
  - Start-up and long term costs of Central IRB infrastructure
  - The confusion resulting from Institution-specific assignation of Institutional Responsibility and IRB-review responsibility
  - The critical role that trust and familiarity play in development and negotiation of IRB reliance relationships

Perceived Challenges for the relying sites

- How to provide the required institutional review
  - Who should be involved?
    - The local IRB? The PI? Institutional Officials? Other?
  - What should that review include?
- Determining appropriate ongoing institutional oversight of the research.
  - Once the study is underway – what is our role?
  - Need to maintain HRPP responsibilities
- Supporting researchers' compliance with the CIRB

General Concerns

- Requests/mandates for single IRB review do not adequately address the complexities involved and the resources required
- The many ‘models’ of single IRB review add confusion
  - For the institution
    - Local roles and responsibilities vary by model
  - For the investigators and their staffs

Truly final slide

- The NeuroNEXT CIRB is an experiment within an experiment
  - Hopefully our NeuroNEXT experience can help to inform the process
- The ‘safety net’ of the NN infrastructure may limit the generalizability of lessons learned